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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,045	08/29/2006	**Johannes Auer**	22388	7458

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
06/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,045	AUER ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/06, 8/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are defined in terms of having the CGT codon at particular codon positions. However, the claim does not specifiy that the numbering is according to the sequence shown in Swiss-Prot P14210, wherein amino acids 1-32 denotes signal sequence and amino acids 32-494 denotes alpha chain according to the description at page 2, lines 25-27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl et al. in view of Fuglsang, Olivares-Trejo et al., and Jeh et al.

Stahl et al. discloses high-level recombinant expression of HGF NK1 and NK2 in E. coli (see abstract). On page 765, right column, fourth paragraph NK1 and NK2 are disclosed to accumulate to about 10-20% of the total protein (see also page 2, lines 14 and 15 of the present application). The inclusion bodies are solubilized and the proteins renatured. Stahl et al. does not disclose substituting at least one of the codons at positions 33, 35 and 36 (in claims 1 and 3), or the three codons simultaneously (in claims 2 and 4) by CGT.

Fuglsang discloses the preferred codon usage in Escherichia coli. Table 2 discloses that the most optimal codon for Arg in E. coli is CGT (it has the most negative correlation of RSCU with Nc(AA), and the most positive correlation of RSCU with CAI).

Olivares-Trejo et al. discloses that an increase in the synthesis of a particular protein in E. coli is observed when the rare arginine codons AGA and AGG at positions 3 and 4 are changed to CGT (see abstract, and page 1046, right column, first paragraph), which are exactly the same changes as proposed in claims 1-4 of the present application.

Jeh et al. also discloses an improved production method of flounder growth hormone (fGH) in E. coli. In this method the first 15 codons of the wild type fGH were randomly altered to search for the most optimal expression of fGH. The increase was from a low expression level of 6% to a 25% of the total cell protein (see paragraph bridging left and right columns in page 188). The highly expressing clones included as the

optimal Arg encoding codon, CGT (the same referred to in claims 1 to 4 of the present application) as shown in figure 3 of Jeh et al.

The HGF natural codons at position 33 is AGG, and at positions 35 and 36 is AGA. Both AGG and AGA are shown in Table 2 of Fuglsang not to be optimal codons in E. coli. Thus, the skilled person would have been motivated to substitute the natural codons at positions 33, 35 and 36 by the most optimal codon for Arg, which is CGT, in order to improve expression of the α-chain of HGF or an N-terminal fragment thereof. It would have been obvious to produce the HGF recombinantly using a codon optimized nucleic acid sequence to optimize production. The combined teachings of Stahl et al., Fuglsang, Olivares-Trejo et al., and Jeh et al. would have motivated the skilled person to substitute more preferred arginine codons for the less preferred naturally occurring codons.

Should applicant argue unexpected results with respect to the claimed invention, they are reminded that claims 1-2 are directed to a nucleic acid and not a method of improved production, claims 3-4 are directed to any microbial host cell (not E. coli), and substitution of only one of the codons at positions 33, 35, and 36, may not result in a detectable effect in the expression of NK4 in E. coli (as compared to the expression shown in Stahl et al. by using the standard expression system in E. coli). If no improvement in the expression of the NK4 HGF is shown by mutants having only a single codon substituted then there are no unexpected results. Applicant is reminded that unexpected results must be commensurate in scope to the claims. It is further noted that the present application discloses only one working example where the DNA expression in E. coli of the NK4 has been enhanced: the mutation disclosed in example 1 having SEQ ID NO: 3. As disclosed at page 7 of the specification, said

mutant has the following technical features: (a) Elimination of the eukaryotic signal peptide sequence and fusion of the ATG start codon next to amino acid position 32 of NK4; (b) Exchange of amino acid position 32 (position 2 in SEQ ID NO: 2) from Gln to Ser in order to improve homogeneity of the protein product (Met-free); (c) Modification of the DNA sequence of the codons of amino acids at position 33 (AGG to CGT), 35 (AGA to CGT), and 36 (AGA to CGT) in order to improve gene expression in E. coli; (d) Modification of the DNA sequence of codons at position 477 (ATA to ATC) and 478 (GTC to GTT) in order to facilitate insertion of PCR product into the vector; and (e) Introduction of two translational stop codons at positions 479 (TAA) and 480 (TAG), in order to stop the translation at a position equivalent to the end of NK4 protein domain. Many of these mutations are not limitations of the claims and might contribute to the level of production seen. Unexpected results commensurate in scope to the claims (including the breadth of N-terminal fragments and microbial host cells embraced) would need to be demonstrated.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa